Published in final edited form as:

Respir Physiol Neurobiol. 2013 November 1; 189(2): . doi:10.1016/j.resp.2013.05.025.

Common mechanisms of compensatory respiratory plasticity in spinal neurological disorders

Rebecca A. Johnson^a and Gordon S. Mitchell^b

^aDepartment of Surgical Sciences, University of Wisconsin, 2015 Linden Drive, Madison, WI, 53706

^bDepartment of Comparative Biosciences, University of Wisconsin, 2015 Linden Drive, Madison, WI, 53706

Abstract

In many neurological disorders that disrupt spinal function and compromise breathing (e.g. ALS, cervical spinal injury, MS), patients often maintain ventilatory capacity well after the onset of severe CNS pathology. In progressive neurodegenerative diseases, patients ultimately reach a point where compensation is no longer possible, leading to catastrophic ventilatory failure. In this brief review, we consider evidence that common mechanisms of compensatory respiratory plasticity preserve breathing capacity in diverse clinical disorders, despite the onset of severe pathology (e.g. respiratory motor neuron denervation and/or death). We propose that a suite of mechanisms, operating at distinct sites in the respiratory control system, underlies compensatory respiratory plasticity, including: 1) increased (descending) central respiratory drive, 2) motor neuron plasticity, 3) plasticity at the neuromuscular junction or spared respiratory motor neurons, and 4) shifts in the balance from more to less severely compromised respiratory muscles. To establish this framework, we contrast three rodent models of neural dysfunction, each posing unique problems for the generation of adequate inspiratory motor output: 1) respiratory motor neuron death, 2) de- or dysmyelination of cervical spinal pathways, and 3) cervical spinal cord injury, a neuropathology with components of demyelination and motor neuron death. Through this contrast, we hope to understand the multilayered strategies used to “fight” for adequate breathing in the face of mounting pathology.

Keywords

respiratory control; spinal cord; demyelination; spinal injury; motor neuron disease

1. Introduction

Precise, yet robust, ventilatory control is critical to maintain adequate ventilation when confronted by everyday physiological challenges, including tasks as simple as walking. This requirement becomes more challenging with the onset of disease, including many neurological disorders that threaten the ability to generate adequate breathing, even at rest.

© 2013 Elsevier B.V. All rights reserved.

Corresponding author: Rebecca A. Johnson, Department of Surgical Sciences, University of Wisconsin, 2015 Linden Drive, Madison, WI 53706, Phone: (608)265485, pipob@svm.vetmed.wisc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Because ventilation is so essential for life, unique properties may be expected in the respiratory control system that enable its “fight” to preserve adequate breathing.

Patients with severe neurological disorders including multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS) and chronic cervical spinal injury often maintain breathing capacity, despite profound pathology in regions critical for breathing (*e.g.* respiratory motor neuron death or disrupted synaptic inputs to those respiratory motor neurons). As these disorders become severe, limits to compensation may be reached, causing catastrophic ventilatory failure and either ventilator-dependence or death. The rapid onset of ventilatory failure is sometimes startling, and these patients seem to “fall off a cliff.” However, virtually nothing is known concerning how patients compensate for clinical disorders that threaten breathing and mechanisms giving rise to this remarkable spontaneous compensation prior to reaching the “breaking point” when ventilatory failure ensues.

Similar to other neural systems, plasticity is a hallmark of the neural system controlling breathing (Feldman et al., 2003; Mitchell and Johnson, 2003). In recent years, we have come to realize that the capacity for spontaneous and induced respiratory plasticity can be harnessed to treat clinical disorders that severely challenge ventilatory control (Mitchell, 2007). For example, there is a long history demonstrating partial, spontaneous functional recovery of phrenic motor output following cervical spinal hemisection, a phenomenon known as the “crossed phrenic phenomenon” (Goshgarian, 2003). Although the extent of spontaneous functional recovery following cervical hemisection is limited, functional recovery can be greatly enhanced by inducing additional plasticity with, for example, repeated exposure to intermittent hypoxia (Vinit et al., 2009; Dale-Nagle et al., 2010b; Lovett-Barr et al., 2012). In other animal models of clinical disorders, the extent of spontaneous, compensatory respiratory plasticity is more impressive. For example, in a rat model of motor neuron disease, the capacity to generate tidal volume is fully preserved despite substantial death of phrenic and intercostal inspiratory motor neurons (Nichols et al., 2013a).

The fundamental principle guiding this review is that previously unrecognized, common mechanisms of spontaneous, compensatory respiratory plasticity preserve breathing capacity in diverse (but related) clinical disorders that challenge the respiratory system. Here, we will discuss potential sites where this plasticity occurs, and key neurochemicals (*e.g.* serotonin [5-HT] and brain-derived neurotrophic factor [BDNF]) that initiate and orchestrate this plasticity. Potential sites of plasticity include, but are not limited to: 1) increased central respiratory drive, reflected as increased or dispersed activity in bulbospinal pathways, 2) plasticity within respiratory motor neurons, 3) plasticity at the neuromuscular junction (NMJ) and/or respiratory muscles, and 4) shifts in the balance of contributions made by different respiratory muscles to breathing. To make this case, we contrast three rodent models of neural dysfunction, each compromising the ability to generate inspiratory motor output by unique mechanisms: 1) de- or dysmyelination of spinal pathways to respiratory motor neurons, 2) respiratory motor neuron cell death, and 3) cervical spinal cord injury, a neuropathology with components of demyelination and motor neuron death. By contrasting these relatively similar (yet distinct) models, we may provide a conceptual framework to advance our understanding of mechanisms whereby patients compensate for diverse clinical disorders that challenge the control of breathing, including pulmonary, musculoskeletal and neurological disorders. Currently, therapies that improve respiratory motor function in neuropathological disorders are lacking. Greater understanding of endogenous, compensatory mechanisms may suggest innovative targets for future therapeutic interventions directed at restoring breathing capacity.

2. Respiratory compromise in CNS disorders

Respiratory compromise is a pathophysiological feature of many neurological disorders. Although the etiology and precise neurological deficits in the CNS vary between disorders, patients frequently maintain respiratory function well into disease progression. It is nearly impossible to determine if the respiratory system was spared from injury or disease-based pathology in these patients, or if they were somehow able to maintain breathing despite injury/pathology. Below, we review and contrast what is known concerning the extent of respiratory compromise in three separate, yet related human neurological disorders: myelin disorders, ALS, and cervical spinal cord injury. These disorders often contain similar spinal pathology, including elements of spinal demyelination and/or respiratory motor neuron death (Figure 1).

2.1. Myelin Disorders (MS)

According to the Multiple Sclerosis International Foundation, myelin disorders affect over 2 million people worldwide. Primary myelin disorders are divided into two main groups: 1) acquired inflammatory damage to myelin/oligodendrocytes (*e.g.* demyelination; MS) and 2) genetic disorders affecting glia (*e.g.* dysmyelination; leukodystrophies). Abnormal myelination results in disruption of normal synaptic transmission; clinical signs attributable to demyelination are specific to the lesioned sites such as weakness, spastic paresis, ataxia, vision disturbance, and bladder/bowel dysfunction. Inherited, generalized dysmyelination disorders usually manifest early in childhood/infancy and can lead to devastating outcomes such as loss of sight, hearing, speech and mobility, and death may occur within just a few years.

Patients with myelin disorders exhibit breathing abnormalities. For example, with brainstem demyelination, patients may exhibit abnormal respiratory rhythm and pattern, and altered sensory processing of chemoafferent respiratory signals (Newsom-Davis, 1974; Rizvi et al., 1974; Mochizuki et al., 1988; Howard et al., 1992; Miller et al., 2003). Lesions in the cervical spinal cord are associated with ventilatory insufficiency, primarily inspiratory and expiratory muscle weakness (Cooper et al., 1985; Kuwahira et al., 1990; Foglio et al., 1994; Buyse et al., 1997; Mutulay et al., 2005; Fry et al., 2007; Karparkin, 2008). Although mild at first, these respiratory deficits progress in severity, causing significant morbidity and mortality as patients succumb to respiratory or upper airway dysfunction (Redelings et al., 2006; Hirst et al., 2008; Karparkin, 2008). Respiratory dysfunction is due, at least in part, to demyelination of CNS areas involved in normal ventilatory control. Despite the fundamental importance of respiratory dysfunction in the progression of myelin disorders, little is known concerning the mechanisms whereby patients compensate for such changes until the disease becomes sufficiently severe that the patients just “fall off a cliff”.

2.2. ALS

ALS is a fatal degenerative disease characterized by progressive muscle weakness, paralysis and progressive loss of motor neurons (Charcot and Joffroy, 1869; Mayeux et al., 2003). Cases can be sporadic, where the inciting cause is unknown (~90% of cases), or familial, resulting from one of many genetic mutations. The pathogenesis of motor neuron degeneration is a topic of considerable debate (Cleveland and Rothstein, 2001; Cluskey and Ramsden, 2001; Bossy-Wetzel et al., 2004; Bruijn et al., 2004). Patients exhibit clinical signs attributable to both upper and lower motor neuron death, including spasticity, hyperreflexia, swallowing and speaking deficits, peripheral muscle weakness, fasciculations and atrophy (Cleveland and Rothstein, 2001). Respiratory signs occur with loss of upper and spinal motor neurons (Lyll et al., 2001). ALS patients often exhibit central sleep apnea (Bourke et al., 2001; McKay et al., 2005), reduced inspiratory capacity and maximum

voluntary ventilation, and ultimately succumb to profound ventilatory impairment (Fallat et al., 1979; Lyall et al., 2001; Stewart et al., 2001; Ilzecka et al., 2003; Talakad et al., 2009). However, respiratory insufficiency usually occurs well into disease progression; it is not known if this delayed onset of respiratory impairment results from late onset of respiratory motor neuron death, or if the motor neuron death precedes respiratory impairment since it has not been possible to obtain motor neuron counts prior to patient death. Rodent studies suggest the striking possibility that breathing capacity may continue unimpaired until late in the progression of respiratory motor neuron death.

2.3. Spinal cord injury

Human cervical spinal injuries (especially above spinal segment C₃) frequently cause respiratory insufficiency as neural pathways to respiratory motor neurons are disrupted. Loss of neural pathways may result directly from mechanical trauma, or from events secondary to the inflammatory cascade following injury, including demyelination from oligodendrocyte cell death (Emery and Cochrane, 1988; Casha et al., 2001; Ye et al., 2012). Although some individuals die immediately after high cervical injury (before ventilatory support can be obtained), other patients survive the initial injury and then develop symptoms as the inflammatory cascade ensues.

Most patients improve respiratory (and locomotor) functions to some degree within one year of injury, likely due to plasticity in spared axonal pathways (Mansel and Norman, 1990). Unfortunately, the 1-year survival rate of ventilator-dependent patients is only 25% (DeVivo and Ivie, 1995), and the most common cause of death after spinal cord injury is respiratory failure (Frankel et al., 1998). Mechanisms whereby patients compensate for and even improve impaired motor function following severe spinal injury are not well understood. Nor has the “trigger” been identified when patients decompensate and progress to ventilatory failure.

3. Rodent models of respiratory compromise in neurological disorders

3.1. Myelin disorders (dysmyelination and demyelination)

To study the complex process of myelination and the physiological (ventilatory) consequences of de- or dysmyelination, groups of rodents with inducible (*e.g.* chemical demyelination) and genetic disorders were developed (Radtke et al., 2007). Although respiratory insufficiency has seldom been studied in any of these models, respiratory dysfunction has been implicated in the death of the myelin-deficient (*md*) rat, which has a mutation in the proteolipid protein gene required for generalized CNS myelination (Lunn et al., 1995). Hypoxic ventilatory responses were depressed in juvenile *md* rats, and several died during hypoxic exposures (Miller et al., 2003), leading the authors to conclude that rats died from abnormal central processing of chemo-afferent neural inputs from the peripheral chemoreceptors. In addition, recent studies suggest that young, adult *les* rats with generalized CNS dysmyelination due to an autosomal recessive mutation in the required myelin basic protein gene (Lunn et al., 1995; Kwiecien et al., 1998) maintain ventilatory capacity at baseline breathing and during respiratory challenge. However, with age, they appear to “fall off a cliff” as ventilatory capacity becomes compromised, phrenic nerve activity becomes dyscoordinated, and the capacity to generate normal phrenic nerve activity becomes impaired (Johnson et al., 2010).

Although human myelin disorders can present with *generalized* dysmyelination, including dysmyelination of respiratory-related spinal pathways, diseases such as MS are often associated with *focal* CNS demyelination with corresponding clinical signs. Thus, inducible demyelination techniques have been developed to produce focal lesions. Experimental autoimmune encephalomyelitis (EAE) in rodents, induced by immunization with a myelin

antigen, has many similarities to human MS due to its inflammatory nature and multifocal lesion distribution. But unpredictable lesion location and timing make it difficult to investigate deficiencies in specific demyelinated pathways. Intraspinal ethidium bromide (EB) injection is a commonly used model of CNS demyelination directed at specific spinal tracts (Blakemore, 1982; Graça and Blakemore, 1986; Jeffery and Blakemore, 1997; Blakemore and Franklin, 2008; Mothe and Tator, 2008; Lee et al., 2010). In the EB model, oligodendrocytes show toxic signs within 24 hrs, causing extensive demyelination and limited axonal degeneration 7–14 days post-injection (Blakemore, 1982; Jeffery and Blakemore, 1997; Blakemore and Franklin, 2008). Unilateral EB injections at spinal segment C₂ demyelinate 22±5% (mean±SEM) of white matter and minimally affect ventilatory capacity (Nichols et al., 2012). However, phrenic nerve activity ipsilateral to the lesion is significantly impaired (Nichols et al., 2012; Figure 2). Bilateral lesions demyelinate 53±9% (mean±SEM) of white matter, but also have little effect on ventilation (Johnson and Mitchell, unpublished observations). Thus, spontaneous compensatory plasticity maintains breathing in the face of severe disruption in neural pathways to phrenic motor neurons, thereby impairing phrenic motor output. On the other hand, the observation that the capacity to increase phrenic nerve activity is impaired, yet the capacity to increase tidal volume is not, suggests a degree of spontaneous compensatory plasticity at sites apart from the phrenic motor nucleus; tidal volume must be preserved by mechanisms at the NMJ or respiratory muscles, or by shifts to less affected respiratory motor pools (*e.g.* intercostal muscles).

EB-induced demyelination is reversible; Schwann cells are present by 7 days post-injection and extensive spontaneous remyelination is observed 2 weeks post-EB (Blakemore, 1982; Graça and Blakemore, 1986; Sallis et al., 2006; Bondan et al., 2010; Nichols et al., 2012). Consistent with the time course of spontaneous remyelination, phrenic nerve activity returns to pre-injection levels by 14 days, providing a model to study the reversibility of endogenous compensatory mechanisms (Nichols et al., 2012).

3.2. ALS (motor neuron death)

Genetic rodent models have been developed to investigate pathogenic mechanisms underlying motor neuron degeneration and functional deficits associated with motor neuron loss. Although only a fraction of human ALS cases are associated with genetic mutations, rodent models with mutations in the SOD1 enzyme exhibit a similar disease progression to patients with familial and sporadic ALS (Wong et al., 1995; Liu et al., 1999; Nagai et al., 2001; Howland et al., 2002; Bruijn et al., 2004). However, whether or not this genetic model faithfully recapitulates all aspects of human sporadic ALS, it does cause respiratory motor neuron cell death (Nichols et al., 2013a), providing an important model to study compensatory respiratory plasticity when confronted with motor neuron death. SOD1^{G93A} rats exhibit profound respiratory motor neuron degeneration at disease end-stage (~60–85% losses of phrenic, ~45–55% losses of T₅ intercostal motor neurons; Nichols et al., 2013a). In association, phrenic nerve activity and compound diaphragm action potentials are significantly impaired at end-stage (Lladó et al., 2006; Nichols et al., 2013a; Figure 2). However, despite these major losses of respiratory motor neurons and motor output, ventilatory capacity is completely preserved (Nichols et al., 2013a; Figure 2). We suspect that only a few days later, these same rats would succumb to respiratory failure and die (Note: end-stage is defined by a 20–30% decrease in body mass *versus* spontaneous death) since mice overexpressing SOD1^{G93A} preserve breathing capacity completely, and then exhibit precipitous ventilatory failure two days later (Tankersley et al., 2007). Unfortunately, there was no estimate of respiratory motor neuron numbers in the mouse study. Both SOD1^{G93A} rats and mice appear to preserve breathing capacity well after the onset of limb paralysis, despite similar (at least overlapping) progression in the death of motor neurons innervating relevant muscles (Nichols et al., 2013a). Thus, it is interesting to note that

human ALS patients often maintain respiratory function well after the onset of paralysis in arms or legs (Lyll et al., 2001; Pinto et al., 2009). It would be of considerable interest to know the patterns of respiratory motor neuron death as ALS progresses in humans.

A novel, inducible rodent model of specific respiratory motor neuron death was recently developed in our laboratory (Nichols et al., 2013b) and involves the use of saporin conjugated to cholera toxin B fragment to selectively target and destroy respiratory motor neurons. When injected into muscle, conjugated CTB and saporin are translocated to the cell body innervating that muscle; CTB and saporin then dissociate and the liberated saporin inactivates ribosomes, thereby killing the neuron over many hours-to-days (Sperti et al., 1973; Barbieri et al., 1992; Bolognesi et al., 1996; Llewellyn-Smith et al., 1999; Llewellyn-Smith et al., 2000). In preliminary studies, intrapleural CTB-S destroys phrenic (and intercostal motor neurons) in a dose-dependent manner (Nichols et al., 2013b). Thus, CTB-S injection represents a stable and selective model to study the impact of respiratory motor neuron death on ventilation, phrenic nerve activity, and compensatory respiratory plasticity.

3.3. Cervical spinal cord injury (cSCI)

cSCI involves axotomy and/or demyelination in neural pathways innervating respiratory motor neurons as well as some motor neuron death (particularly with mid-cervical injuries). Two models of cSCI that differ significantly in lesion pathology have frequently been used to study respiratory impairment after injury: cervical contusions (C₄, C₅, or both) and C₂ hemisection (C₂HS) (Norenberg et al., 2004; Siegenthaler et al., 2007; Nicaise et al., 2012a, 2012b). Spontaneous functional recovery of breathing capacity has most often been studied after C₂HS (Goshgarian, 2003); C₂HS permanently disrupts at least half of the spinal descending pathways, and rats exhibit persistent deficits in ventilatory capacity (Fuller et al., 2006). Although the extent of spontaneous functional respiratory recovery is slow and frustratingly limited, a small, but ineffective level of phrenic motor output does eventually return, mainly through enhancement of crossed-spinal pathways (Fuller et al., 2006; Dougherty et al., 2012).

Recent studies have addressed breathing deficits after cervical contusion injuries, which have more variable effects on the specific descending pathways affected, but more closely mimic common spinal injuries in humans (Golder et al., 2011; Lane et al., 2012; Nicaise et al., 2012a, 2012b). In addition to potential axotomy, contusion injuries cause white matter apoptosis, demyelination, and robust macrophage responses extending several millimeters from the epicenter (Siegenthaler et al., 2007). Mid-cSCI can also cause variable degrees of phrenic motor neuron death (Lane et al., 2012). Remarkably, unilateral C₄ contusion injuries show nearly complete spontaneous recovery of breathing capacity by 14 days post-injury despite persistent deficits in phrenic motor output or diaphragm activity ipsilateral to the injury (Golder et al., 2011; Lane et al., 2012; Figure 2). Consistent with these studies, unilateral C₄-C₅ contusion injuries result in phrenic motor neuron loss and white matter degeneration, phrenic nerve axonal degeneration, reduced diaphragm compound action potentials, and denervation followed by partial reinnervation at the diaphragm NMJs 2 weeks post-injury (Nicaise et al., 2012a, 2012b). Although spontaneous diaphragm electromyogram (EMG) amplitude was not affected by contusion injury, burst frequency was significantly reduced and duration was prolonged 6 weeks post-injury (Nicaise et al., 2012a, 2012b). Altogether, these studies suggest that rodents maintain ventilation in the face of significant damage to spinal respiratory-related neural pathways. Mechanisms underlying this remarkable spontaneous compensation are not known.

4. With compromised phrenic motor output, how is breathing maintained?

Based on these considerations of human patients, and studies of rodent disease models, we are left with a fundamental question: If severe pathology disrupts flow of information to respiratory motor neurons, how is it possible to generate a normal, maximal breath? We propose that rodents (and humans) use a comprehensive, multilayered strategy to compensate for severe CNS pathology, thereby preserving breathing capacity. If these compensatory mechanisms are not utilized, the respiratory control system would surely fail. Figure 3 represents several potential mechanisms that may preserve ventilatory capacity despite severe deficiencies in phrenic motor output: (1) increased central respiratory drive to spared motor neurons, (2) plasticity within respiratory motor neurons, (3) increased NMJ and/or respiratory muscle plasticity, and (4) shifts in emphasis from the diaphragm to less-used respiratory motor neuron pools.

4.1. Increased central respiratory drive (1)

Although respiratory rhythm generation and pattern formation originate within the ventrolateral medulla (Feldman et al., 2013), regulation of central respiratory drive to respiratory motor neurons occurs at multiple levels. Many types of sensory inputs affect respiratory motor output, including afferent information from carotid chemoreceptors (Kumar and Prabhakar, 2007; Prabhakar, 2011), pulmonary stretch receptors (Brouns et al., 2012), and central (ventral brainstem) chemoreceptor (mainly CO₂-sensitive) afferents (Richerson et al., 2005; Corcoran et al., 2009; Guyenet, 2010). Collectively, these afferent signals modulate the respiratory network generating respiratory rhythm and pattern formation (Feldman et al., 2013). Brainstem pre-motor neurons of the ventral respiratory group send descending axons to spinal respiratory (phrenic and inspiratory intercostal) motor neurons, ultimately generating a breath. Central respiratory drive may be augmented (or reduced) by sensory feedback at the spinal level, including (for example) feedback from muscle spindle afferents (Critchlow and von Euler, 1963; Aminoff and Sears, 1971). Any persistent stimulus acting through these sensory systems (*e.g.* chronic hypoxia or hypercapnia) associated with disease can maintain normal breathing levels within the diminished capacity, but cannot increase the capacity for breathing.

In the clinical disorders discussed here, modulation of sensory inputs is another possible means of preserving breathing at levels below a diminished capacity. However, again, brainstem modulation/plasticity will not restore the capacity to increase breathing, at least not without additional mechanisms operating at or below (*i.e.* downstream) from the site of pathology. In addition, we speculate that compensatory mechanisms involving increased central neural respiratory drive could lead to dyspneic sensations due to corollary discharge (*i.e.* ascending signals to thalamic and cortical circuits underlying dyspneic sensation; Lansing et al., 2009). On the other hand, compensatory mechanisms principally involving the spinal cord and/or neuromuscular junction might preserve ventilation without producing the same degree of corollary discharge and dyspnea.

The neurochemicals 5-HT and BDNF regulate respiratory activity at multiple brainstem sites involved in respiratory control (Katz, 2003, 2005; Hodges and Richerson, 2010). However, their impact is more likely to be associated with breathing pattern and stability *versus* the magnitude of respiratory motor output. 5-HT is implicated in states that exhibit ventilatory instability, such as periodic breathing or sleep apnea (Benarroch 2007; Dempsey et al., 2010; Lovering et al., 2012). Decreased brainstem BDNF is associated with severe respiratory rhythm abnormalities during Rett syndrome (Chahrour and Zoghbi, 2007; Ogier and Katz, 2008). The instability of breathing in Rett syndrome is at least partially ameliorated by agonists for the high affinity BDNF receptor, TrkB (Johnson et al., 2012; Schmid et al., 2012). Modulation and/or plasticity in central respiratory drive upstream from

respiratory motor neurons have not been studied in myelin disorders, primary motor neuron disease, and/or spinal cord injury.

4.2. Plasticity in phrenic motor nuclei (2)

Phrenic motor facilitation (PMF) and phrenic long-term facilitation (pLTF) are two forms of inducible spinal respiratory plasticity that increase the efficacy of synaptic inputs to respiratory motor neurons (Dale-Nagle et al., 2010a). PMF results from the activation of diverse neurochemical pathways including: spinal adenosine 2A (Golder et al., 2008), 5-HT (MacFarlane and Mitchell., 2009; Hoffman and Mitchell, 2011; MacFarlane et al., 2011), alpha-1 adrenergic (Dale-Nagle et al., 2010a), erythropoietin (Dale et al., 2012) or vascular endothelial growth factor application (Dale-Nagle et al., 2011). pLTF is a specific form of PMF observed following acute intermittent hypoxia *via* a mechanism that requires spinal activation of 5-HT₂ receptors, new synthesis of BDNF and subsequent TrkB activation and then signaling *via* ERK MAP kinases (Hoffman et al., 2012). Although the specific relevance of these distinct mechanisms of PMF to the disease states considered here is uncertain, they each have the potential to up-regulate motor neuron function, thereby restoring lost capacity to increase phrenic (or other respiratory) motor neuron output.

Although ventilatory capacity is well-maintained in the SOD1^{G93A} rat, phrenic nerve output is significantly reduced (Nichols et al., 2013a; Figure 2). On the other hand, the reduction in phrenic motor output during maximal chemoreceptor stimulation does not match the severity of phrenic motor neuron death. Thus, plasticity may arise at the level of phrenic motor neurons, thereby contributing to a relative preservation of phrenic motor output (Nichols et al., 2013a). Nevertheless, there is some degradation of the capacity to generate phrenic motor output at the end-stage defined in the study of Nichols and colleagues (2013a). In association, multiple proteins necessary for intermittent hypoxia-induced phrenic motor plasticity are expressed at increased levels in spared phrenic motor neurons (Satriotomo and Mitchell, unpublished observations), suggesting that neurochemical plasticity within phrenic motor neurons prolonged the survival and/or activity of surviving motor neurons.

Diminished phrenic motor output could be reversed in the study of Nichols and colleagues (2013a) by: 1) slowing phrenic motor neuron death by injecting neural progenitor (stem) cells into the region of the phrenic motor nucleus before disease onset, or 2) inducing pLTF with acute intermittent hypoxia at disease end-stage. Thus, inducible spinal plasticity within the phrenic motor nucleus amplifies motor output from surviving neurons, thereby restoring lost capacity to generate phrenic nerve activity.

Following EB-induced spinal demyelination of pathways to respiratory motor neurons, the same pattern prevails: phrenic motor output is substantially decreased, yet ventilation is virtually unaffected (Nichols et al., 2012; Figure 2). Similar to ALS, spontaneous compensatory mechanisms upstream from the phrenic motor nucleus are unlikely to preserve breathing capacity in this disease model. As the affected spinal pathways remyelinate with time, the capacity to increase phrenic motor output returns to normal levels (Nichols et al., 2012).

Unpublished, preliminary data from our laboratory suggest that EB-induced spinal demyelination is not met with similar compensatory plasticity in heterozygous BDNF knock-out rats. In contrast to wild-type rats, heterozygous knock-outs exhibit decreased ability to generate respiratory volumes 7 days post-EB injection (Johnson and Mitchell, unpublished observations). BDNF rescues axotomized motor neurons (Sendtner et al., 1992; Yan et al., 1992; Gimenez y Ribbotta et al., 1997; Zhou and Shine, 2003) and promotes myelination of regenerated axons (McTigue et al., 1998). Thus, in these preliminary studies, the lack of normal BDNF levels may undermine spontaneous remyelination and/or

mechanisms of compensatory respiratory motor plasticity. However, in these studies, the precise location of BDNF effects on ventilatory capacity is not known. For example, the relevant BDNF may be in the motor neuron pool, the NMJ or the muscle itself (Zhan et al., 2003).

In rodent models of spinal injury, the respiratory system exhibits considerable ability to compensate, preserving ventilatory capacity despite severe disruption of descending neural pathways, myelination, or motor neuron survival (Brown et al., 2006; Goshgarian, 2009; Sieck and Mantilla, 2009; Golder et al., 2011; Dougherty et al., 2012; Lane et al., 2012). Although phrenic nerve output remains nearly absent for some time after spinal contusion injuries, breathing recovers progressively and reaches nearly normal levels by 14 days post-injury (Golder et al., 2011; Figure 2). In contrast, C₂HS causes more enduring functional deficits. In this model, an initial decrease in breathing capacity is followed by partial recovery; however, persistent deficits remain for over two months post C₂HS (Fuller et al., 2006). The lack of spontaneous recovery in breathing capacity does not mean that breathing capacity cannot be restored in hemisectioned rats. Following C₂HS, acute intermittent hypoxia-induced pLTF initially disappears (2 weeks), but then recovers progressively over 8 weeks post-injury as serotonergic innervation of phrenic motor neurons returns (Golder and Mitchell, 2005). At 8 weeks post-injury, even a single presentation of acute intermittent hypoxia restores normal baseline levels of phrenic nerve activity. Further, by repetitive exposure to acute intermittent hypoxia, breathing capacity can be fully restored to normal, even at 2 weeks post- C₂HS (Lovett-Barr et al., 2012). The reasons full functional recovery does not occur in this model without additional stimulation are not clear, but there may be clues in the type of injury (hemisection) which removes some descending modulatory influences completely on the side of the injury.

Following contusion injuries, greater capacity for spontaneous compensatory plasticity has been reported (Golder et al., 2011; Lane et al., 2012; Figure 2). In rats with mid-cervical spinal injuries, breathing capacity returns completely to normal, yet phrenic nerve activity is still impaired. Again, these observations suggest that mechanisms beyond brainstem and/or spinal plasticity in descending pathways to respiratory motor neurons must be involved in overall ventilatory compensation for spinal disease or injury. Possible “downstream” mechanisms are discussed below.

4.3. NMJ or respiratory muscle plasticity (3)

Plasticity downstream from respiratory motor neurons appears to be a crucial property of the respiratory control system and is reviewed elsewhere within this special issue (Sieck and Mantilla, *ibid*). Patients with neurological disorders frequently have respiratory muscle weakness, both from their primary CNS pathology and from neuromuscular deterioration. For example, respiratory muscle atrophy and NMJ degeneration are significant pathologies in ALS; they may arise secondary to motor neuron degeneration, or may exacerbate motor neuron death (*i.e.* dying back hypothesis; for review: Krakora et al., 2012). Compensatory mechanisms likely mask NMJ loss until late in disease progression. Although compensatory mechanisms may be multilayered and complex (Figure 3), plasticity at the NMJ or muscle may nevertheless play a critical role in respiratory compensation in rodent models of ALS (Krakora et al., 2012).

Patients with myelin disorders also exhibit inspiratory and expiratory muscle weakness (Cooper et al., 1985; Foglio et al., 1994; Buyse et al., 1997; Mutulay et al., 2005; Fry et al., 2007; Karparkin, 2008). Although muscle weakness is likely due to impaired central synaptic drive from the demyelination of central pathways, changes at the NMJ or respiratory muscles themselves may also contribute to, or compensate for these deficits.

However, the relative contributions of neuromuscular *versus* neural dysfunction in central myelin disorders is not known, and NMJ or muscle plasticity have not been investigated.

Muscle or NMJ plasticity may also contribute to functional recovery after spinal injury (Mantilla et al., 2004; Mantilla and Sieck, 2009). In rodents, cervical contusions are associated with reduced diaphragm compound action potentials, and denervation is followed by partial reinnervation at the diaphragm NMJs by 2 weeks post-injury (Nicaise et al., 2012a, 2012b). Evidence suggests structure-activity relationships between NMJs and diaphragm muscle fibers, and that phrenic motor units can be differentially recruited during different behaviors (Mantilla and Sieck, 2011; Sieck et al., 2012). Collectively, these studies suggest that plasticity in discrete motor units may occur, depending on which fiber types or NMJs are injured, and may be differentially affected based on the motor activity required (*i.e.* breathing *versus* coughing). Further investigation of these issues is warranted.

4.4. Shifts in contributions from respiratory motor neuron pools (4)

A likely mechanism contributing to compensatory respiratory plasticity with spinal injury/disease is an emergent property of the first three mechanisms: a shift in the relative contributions of respiratory motor pools/muscles from more to less compromised motor pools. For example, when phrenic motor neurons are ineffective, there may be a shift in balance to accessory respiratory motor neurons/muscles (*e.g.* inspiratory intercostals). Although the diaphragm is generally regarded as the primary muscle of inspiration, accessory muscles are sufficient to maintain adequate breathing at rest without phrenic/diaphragm contributions (Maskrey et al., 1992). Intercostal motor neurons receive respiratory drive from propriospinal interneurons, which in turn, receive bulbospinal respiratory-related synaptic inputs (De Troyer et al., 2005; Saywell et al., 2011). Indeed, motor unit synchronization occurs across the diaphragm and external intercostal muscles (Rice et al., 2011). Following bilateral phrenicotomy, external intercostal EMG amplitude increases (Sherrey and Megirian, 1990), suggesting that accessory muscles compensate for the loss of diaphragm function.

Inspiratory intercostal motor neurons exhibit greater relative capacity for plasticity (*e.g.* LTF) *versus* phrenic motor neurons (Fregosi and Mitchell, 1994; Navarette-Opazo and Mitchell, unpublished observations). Such plasticity may shift the functional emphasis from the diaphragm to the underutilized intercostal motor neuron pool, thus enabling patients to compensate for a variety of neuromuscular diseases/disorders that challenge the respiratory system (*i.e.* myelin disorders, spinal injury). Such compensation may be less likely in ALS since respiratory motor neuron death occurs in both phrenic and intercostal motor neuron pools (Nichols et al., 2013a). However, to date, definitive studies concerning relative contributions of various respiratory motor pools to ventilatory capacity in any clinical disorder have not yet been performed.

5. Mechanisms of compensatory plasticity in other diseases/disorders

Respiratory compromise is associated with many neurological as well as pulmonary diseases. For example, many patients with neurological or neuromuscular disorders such as Rett syndrome (Katz et al., 2009; Schmid et al., 2012), Down syndrome (Pandit and Fitzgerald, 2012), Alzheimer's disease (Daulatzai, 2012), Parkinson's disease (Pal et al., 2007), Pompe disease (Mellies and Lofaso, 2009), muscular dystrophy and spinal muscular atrophy (Schroth, 2009), and obstructive sleep apnea (Dempsey et al., 2010) all present with some form of ventilatory impairment, and many ultimately succumb to ventilatory failure. Lung diseases, such as chronic obstructive pulmonary disease (COPD; Barreiro and Sieck, 2013; Mantilla and Sieck, 2013) or pulmonary fibrosis also undermine the ability to generate adequate inspiratory volume due to deteriorating mechanics and gas exchange. Although

each of these disorders arises from a distinct etiology, they all share at least one common feature: impaired ability to generate adequate inspiratory volume *via* normal mechanisms. We suspect that, regardless of the primary etiology, the suite of compensatory mechanisms proposed here will be invoked to protect breathing capacity to the greatest extent possible. We propose a unifying hypothesis that these common mechanisms successfully defend breathing capacity in many different clinical disorders that provide a wide range of challenges to the respiratory control system. Although there is evidence for impressive success, for example preserving breathing capacity despite major losses of respiratory motor neurons in motor neuron disease (Nichols et al., 2013), the challenge will eventually be too great (too few motor neurons left, severely impaired lung mechanics, etc.) and the system will fail, leading to catastrophic ventilatory failure.

Many of the clinical disorders listed above are associated with systemic and/or neuro-inflammation. For example, systemic inflammation is associated with obstructive sleep apnea (Gozal, 2009), chronic lung disease (Stockley, 2009; Mantilla and Sieck, 2013) and traumatic, ischemic, and degenerative neural disorders (Teeling and Perry, 2009). Inflammation greatly affects synaptic transmission and plasticity, inducing plasticity in some cases and undermining it in others (Di Filippo et al., 2008). We have recently come to realize that systemic inflammation profoundly impairs respiratory plasticity following intermittent hypoxia (Huxtable et al., 2011; Vinit et al., 2011; Huxtable et al., 2013).

6. Summary

We address a fundamental question concerning respiratory function in diverse clinical disorders that challenge the control of breathing. At least in some cases, the respiratory control system mounts sufficient compensatory responses to preserve full ventilatory capacity, with few if any overt clinical respiratory signs until late in disease progression. However, once pathology becomes too severe, limits of compensation are reached, resulting in catastrophic ventilatory failure. For example, ALS patients often sustain breathing until their body is nearly completely paralyzed, and then seemingly “fall off a cliff” into respiratory failure.

Here, we propose that such impressive respiratory plasticity results from a comprehensive, multilayered strategy to compensate for severe CNS pathology, thereby protecting the one motor behavior most necessary for life – breathing. Although investigations concerning compensatory respiratory plasticity are just beginning, we are starting to elucidate some of the sites, and individual mechanisms that may play important roles. We consider the respective contributions of plasticity in: 1) bulbospinal respiratory drive to motor neurons, 2) respiratory motor neuron plasticity *per se*, 3) NMJ and/or respiratory muscle plasticity, and 4) the three prior mechanisms converging to shifts in the balance of contributions from different respiratory motor pools and muscles (shifting from more to less impaired muscles). We have a long way to go before we will fully understand compensatory respiratory plasticity in injury or disease, the range of diseases where this multilayered strategy contributes, and factors that promote or undermine its efficacy (*e.g.* inflammation).

These studies will lay the foundation for future therapeutic interventions that may slow the progression of or even reverse respiratory impairment associated with neurological diseases. For example, stem cell therapies directed at providing neurotrophic support to neurons or glia enhance respiratory motor activity associated with motor disease (Nichols et al., 2013a). In addition, non-invasive interventions such as intermittent inspired hypoxia improve respiratory function in spinally-injured humans (Lovett-Barr et al., 2012; Trumbower et al., 2012; Nichols et al., 2013a). Newer therapeutic interventions directed at regulating apoptosis and excitotoxicity, neuroinflammation, and axonal or glial trophism or inhibition,

including nanoparticle-based approaches have shown promise in reducing clinical signs associated with spinal disorders (for review see Duncan, 2008; Huang and Franklin, 2012; Varma et al., 2013). However, these have not been specifically directed at improving respiratory function in spinal neurological disease at this time.

References

- Aminoff MJ, Sears TA. Spinal integration of segmental, cortical and breathing inputs to thoracic respiratory motoneurons. *J Physiol.* 1971; 215(2):557–575. [PubMed: 4336048]
- Barbieri L, Ferreras JM, Barraco A, Ricci P, Stirpe F. Some ribosome-inactivating proteins depurinate ribosomal RNA at multiple sites. *Biochem J.* 1992; 286:1–4. [PubMed: 1520257]
- Barreiro E, Sieck GC. Muscle dysfunction in COPD. *J Appl Physiol.* 2013 Epub ahead of print.
- Benarroch EE. Brainstem respiratory control: substrates of respiratory failure of multiple system atrophy. *Mov Disord.* 2007; 22(2):155–161. [PubMed: 17133520]
- Blakemore WF. Ethidium bromide induced demyelination in the spinal cord of the cat. *Neuropathol Appl Neurobiol.* 1982; 8(5):365–375. [PubMed: 7177337]
- Blakemore WF, Franklin RJ. Remyelination in experimental models of toxin-induced demyelination. *Curr Top Microbiol Immunol.* 2008; 318:193–212. [PubMed: 18219819]
- Bolognesi A, Tazzari PL, Olivieri F, Polito L, Falini B, Stirpe F. Induction of apoptosis by ribosome-inactivating proteins and related immunotoxins. *Int J Cancer.* 1996; 68:349–355. [PubMed: 8903477]
- Bondan EF, Lallo MA, Martins MFM, Graça DL. Schwann cell expression of an oligodendrocyte-like remyelinating pattern after ethidium bromide injection in the rat spinal cord. *Arq Neuropsiquiatr.* 2010; 68(5):783–787. [PubMed: 21049194]
- Bossy-Wetzel E, Schwarzenbacher R, Lipton SA. Molecular pathways to neurodegeneration. *Nat Med.* 2004; 10:S2–S9. [PubMed: 15272266]
- Bourke SC, Shaw PJ, Gibson GJ. Respiratory function vs. sleep-disordered breathing as predictors of QOL in ALS. *Neurology.* 2001; 57(11):2040–2044. [PubMed: 11739823]
- Brouns I, Pintelon I, Timmermans JP, Adriaensen D. Novel insights in the neurochemistry and function of pulmonary sensory receptors. *Adv Anat Embryol Cell Biol.* 2012; 211:1–115. [PubMed: 22128592]
- Brown R, DiMarco AF, Hoit JD, Garshick E. Respiratory dysfunction and management in spinal cord injury. *Respir Care.* 2006; 51:853–868. discussion 869–870. [PubMed: 16867197]
- Bruijn LI, Miller TM, Cleveland DW. Unraveling the mechanisms involved in motor neuron degeneration in ALS. *Annu Rev Neurosci.* 2004; 27:723–749. [PubMed: 15217349]
- Buyse B, Demedts M, Meekers J, Vandegaer L, Rochette F, Kerkhofs L. Respiratory dysfunction in multiple sclerosis: a prospective analysis of 60 patients. *Eur Respir J.* 1997; 10:139–145. [PubMed: 9032506]
- Casha S, Yu WR, Fehlings MG. Oligodendroglial apoptosis occurs along degenerating axons and is associated with FAS and p75 expression following spinal cord injury in the rat. *Neuroscience.* 2001; 103(1):203–218. [PubMed: 11311801]
- Charcot J, Joffroy A. Deux cas d'atrophie musculaire progressive avec lesion de la substance grise et des faisceaux antero-latéraux de la moelle epiniere. *Arch Physiol Norm Path.* 1869; 2:745–760.
- Chahrouh M, Zoghbi HY. The story of Rett syndrome: from clinic to neurobiology. *Neuron.* 2007; 56(3):422–437. [PubMed: 17988628]
- Cleveland DW, Rothstein JD. From Charcot to Lou Gehrig: deciphering selective motor neuron death in ALS. *Nat Rev Neurosci.* 2001; 2(11):806–819. [PubMed: 11715057]
- Cluskey S, Ramsden DB. Mechanisms of neurodegeneration in amyotrophic lateral sclerosis. *Mol Pathol.* 2001; 54(6):386–392. [PubMed: 11724913]
- Cooper CB, Trend P St J, Wiles CM. Severe diaphragm weakness in multiple sclerosis. *Thorax.* 1985; 40:633–634. [PubMed: 4035638]

- Corcoran AE, Hodges MR, Wu Y, Wang W, Wylie CJ, Deneris ES, Richerson GB. Medullary serotonin neurons and central CO₂ chemoreception. *Respir Physiol Neurobiol.* 2009; 168(1–2):49–58. [PubMed: 19394450]
- Critchlow V, von Euler C. Intercostal muscle spindle activity and its motor control. *J Physiol.* 1963; 168:820–847. [PubMed: 14072860]
- Dale EA, Mitchell GS. Spinal vascular endothelial growth factor (VEGF) and erythropoietin (EPO) induced phrenic motor facilitation after repetitive acute intermittent hypoxia. *Respir Physiol Neurobiol.* 2013; 185(3):481–488. [PubMed: 23128070]
- Dale EA, Satriotomo I, Mitchell GS. Cervical spinal erythropoietin induced phrenic motor facilitation via extracellular signal-regulated protein kinase and Akt signaling. *J Neurosci.* 2012; 32(17):5973–5983. [PubMed: 22539857]
- Dale-Nagle EA, Hoffman MS, MacFarlane PM, Mitchell GS. Multiple pathways to long-lasting phrenic motor facilitation. *Adv Exp Med Biol.* 2010a; 669:225–230. [PubMed: 20217354]
- Dale-Nagle EA, Hoffman MS, MacFarlane PM, Satriotomo I, Lovett-Barr MR, Vinit S, Mitchell GS. Spinal plasticity following intermittent hypoxia: implications for spinal injury. *Ann NY Acad Sci.* 2010b; 1198:252–259. [PubMed: 20536940]
- Dale-Nagle EA, Satriotomo I, Mitchell GS. Spinal vascular endothelial growth factor induces phrenic motor facilitation via extracellular signal-regulated kinase and Akt signaling. *J Neurosci.* 2011; 31(21):7682–7690. [PubMed: 21613481]
- Daulatzai MA. Dysfunctional nucleus tractus solitarius: its crucial role in promoting neuropathogenetic cascade of Alzheimer's dementia--a novel hypothesis. *Neurochem Res.* 2012; 37(4):846–868. [PubMed: 22219130]
- Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev.* 2010; 90(1):47–112. [PubMed: 20086074]
- De Troyer A, Kirkwood PA, Wilson TA. Respiratory action of the intercostal muscles. *Physiol Rev.* 2005; 85:717–756. [PubMed: 15788709]
- DeVivo MJ, Ivie CS 3rd. Life expectancy of ventilator-dependent persons with spinal cord injuries. *Chest.* 1995; 108(1):226–232. [PubMed: 7606963]
- Di Filippo M, Sarchielli P, Picconi B, Calabresi P. Neuroinflammation and synaptic plasticity: theoretical basis for a novel, immune-centered, therapeutic approach to neurological disorders. *Trends Pharmacol Sci.* 2008; 29(8):402–12.
- Dougherty BJ, Lee KZ, Gonzalez-Rothi EJ, lane MA, Reier PJ, Fuller DD. Recovery of inspiratory intercostal muscle activity following high cervical hemisection. *Respir Physiol Neurobiol.* 2012; 183:186–192. [PubMed: 22705013]
- Duncan ID. Replacing cells in multiple sclerosis. *J Neurol Sci.* 2008; 265(1–2):89–92. [PubMed: 17585942]
- Emery DJ, Cochrane DD. Spontaneous remission of paralysis due to spinal extradural hematoma: case report. *Neurosurgery.* 1988; 23(6):762–764. [PubMed: 3063992]
- Fallat RJ, Jewitt B, Bass M, Kamm B, Norris FH Jr. Spirometry in amyotrophic lateral sclerosis. *Arch Neurol.* 1979; 36(2):74–80. [PubMed: 420626]
- Feldman JL, Mitchell GS, Nattie EE. Breathing: rhythmicity, plasticity, chemosensitivity. *Annu Rev Neurosci.* 2003; 26:239–266. [PubMed: 12598679]
- Feldman JL, Del Negro CA, Gray PA. Understanding the rhythm of breathing: so near yet so far. *Annu Rev Physiol.* 2013; 75:423–452. [PubMed: 23121137]
- Foglio K, Clini E, Facchetti D. Respiratory muscle function and exercise capacity in multiple sclerosis. *Eur Respir J.* 1994; 7:23–28. [PubMed: 8143827]
- Frankel HL, Coll JR, Charlifue SW, Whiteneck GG, Gardner BP, Jamous MA, Krishnan KR, Nuseibeh I, Savic G, Sett P. Long-term survival in spinal cord injury: a fifty year investigation. *Spinal Cord.* 1998; 36(4):266–274. [PubMed: 9589527]
- Fregosi RF, Mitchell GS. Long-term facilitation of inspiratory intercostal activity following carotid sinus nerve stimulation in cats. *J Appl Physiol.* 1994; 477(3):469–479.
- Fuller DD, Golder FJ, Olson EB Jr, Mitchell GS. Recovery of phrenic activity and ventilation after cervical spinal hemisection in rats. *J Appl Physiol.* 2006; 100(3):800–806. [PubMed: 16269524]

- Fry DK, Pfaller LA, Chokshi AR, Wagner MT, Jackson ES. Randomized control trial of effects of a 10-week inspiratory muscle training program on measures of pulmonary function in persons with multiple sclerosis. *J Neurol Phys Ther.* 2007; 31(4):162–172. [PubMed: 18172412]
- Gimenez y Ribbotta M, Revah F, Pradier L, Loquet L, Mallet J, Privat A. Prevention of motoneuron death by adenovirus-mediated neurotrophic factors. *J Neurosci Res.* 1997; 48:281–285. [PubMed: 9160251]
- Golder FJ, Fuller DD, Lovett-Barr MR, Vinit S, Resnick DK, Mitchell GS. Breathing patterns after mid-cervical spinal contusion in rats. *Exp Neurol.* 2011; 231:97–103. [PubMed: 21683697]
- Golder FJ, Mitchell GS. Spinal synaptic enhancement with acute intermittent hypoxia improves respiratory function after chronic cervical spinal cord injury. *J Neurosci.* 2005; 25(11):2925–2932. [PubMed: 15772352]
- Golder FJ, Ranganathan L, Satriotomo I, Hoffman M, Lovett-Barr MR, Watters JJ, Baker-Herman TL, Mitchell GS. Spinal adenosine A2a receptor activation elicits long-lasting phrenic motor facilitation. *J Neurosci.* 2008; 28(9):2033–2042. [PubMed: 18305238]
- Goshgarian HG. The crossed phrenic phenomenon: a model for plasticity in the respiratory pathways following spinal cord injury. *J Appl Physiol.* 2003; 94(2):795–810. [PubMed: 12531916]
- Goshgarian HG. The crossed phrenic phenomenon and recovery of function following spinal cord injury. *Respir Physiol Neurobiol.* 2009; 169:85–93. [PubMed: 19539790]
- Gozal D. Sleep, sleep disorders and inflammation in children. *Sleep Med.* 2009; 10 (Suppl 1):S12–16. [PubMed: 19647481]
- Graça DL, Blakemore WF. Delayed remyelination in rat spinal cord following ethidium bromide injection. *Neuropathol Appl Neurobiol.* 1986; 12:593–605. [PubMed: 3561693]
- Guyenet PG, Stornetta RL, Bayliss DA. Central respiratory chemoreception. *J Comp Neurol.* 2010; 518(19):3883–3906. [PubMed: 20737591]
- Hirst C, Swingle R, Compston DA, Ben-Shlomo Y, Robertson NP. Survival and cause of death in multiple sclerosis: a prospective population-based study. *J Neurol Neurosurg Psychiatry.* 2008; 79(9):1016–1021. [PubMed: 18303108]
- Hodges MR, Richerson GB. Medullary serotonin neurons and their roles in central respiratory chemoreception. *Respir Physiol Neurobiol.* 2010; 173(3):256–263. [PubMed: 20226279]
- Hoffman MS, Mitchell GS. Spinal 5-HT7 receptor activation induces long-lasting phrenic motor facilitation. *J Physiol.* 2011; 589(Pt6):1397–1407. [PubMed: 21242254]
- Hoffman MS, Nichols NL, MacFarlane PM, Mitchell GS. Phrenic long-term facilitation after acute intermittent hypoxia requires spinal ERK activation but not TrkB synthesis. *J Appl Physiol.* 2012; 113(8):1184–1193. [PubMed: 22961271]
- Howard RS, Wiles CM, Hirsch NP, Loh L, Spencer GT, Newsom-Davis J. Respiratory involvement in multiple sclerosis. *Brain.* 1992; 115(2):479–494. [PubMed: 1606478]
- Howland DS, Liu J, She Y, Goad B, Maragakis NJ, Kim B, Erickson J, Kulik J, DeVito L, Psaltis G, DeGennaro LJ, Cleveland DW, Rothstein JD. Focal loss of the glutamate transporter EAAT2 in a transgenic rat model of SOD1 mutant-mediated amyotrophic lateral sclerosis (ALS). *Proc Natl Acad Sci.* 2002; 99(3):1604–1609. [PubMed: 11818550]
- Huang JK, Franklin RJ. Current status of myelin replacement therapies in multiple sclerosis. *Prog Brain Res.* 2011; 201:219–231. [PubMed: 23186717]
- Huxtable AG, Smith SM, Vinit S, Watters JJ, Mitchell GS. Systemic LPS induces spinal inflammatory gene expression and impairs phrenic long-term facilitation following acute intermittent hypoxia. *J Appl Physiol.* 2013; 114(7):879–887. [PubMed: 23329821]
- Huxtable AG, Vinit S, Windelborn JA, Crader SM, Guenther CH, Watters JJ, Mitchell GS. Systemic inflammation impairs respiratory chemoreflexes and plasticity. *Respir Physiol Neurobiol.* 2011; 178(3):482–489. [PubMed: 21729770]
- Ilzecka J, Stelmasiak Z, Balicka G. Respiratory function in amyotrophic lateral sclerosis. *Neurol Sci.* 2003; 24(4):288–289. [PubMed: 14658052]
- Jeffery ND, Blakemore WF. Locomotor deficits induced by experimental spinal cord demyelination are abolished by spontaneous remyelination. *Brain.* 1997; 120:27–37. [PubMed: 9055795]

- Johnson RA, Baker-Herman TL, Duncan ID, Mitchell GS. Ventilatory impairment in the dysmyelinated Long Evans shaker rat. *Neuroscience*. 2010; 169(3):1105–1114. [PubMed: 20542092]
- Johnson RA, Lam M, Punzo AM, Li H, Lin BR, Ye K, Mitchell GS, Chang Q. 7, 8-dihydroxyflavone exhibits therapeutic efficacy in a mouse model of Rett syndrome. *J Appl Physiol*. 2012; 112(5): 704–710. [PubMed: 22194327]
- Karpatkin H. Respiratory changes in multiple sclerosis. *J Neurol Phys Ther*. 2008; 32(2):105. [PubMed: 18645300]
- Katz DM. Neuronal growth factors and development of respiratory control. *Respir Physiol Neurobiol*. 2003; 135(2–3):155–165. [PubMed: 12809616]
- Katz DM. Regulation of respiratory neuron development by neurotrophic and transcriptional signaling mechanisms. *Respir Physiol Neurobiol*. 2005; 149(1–3):99–109. [PubMed: 16203214]
- Katz DM, Dutschmann M, Ramirez JM, Hilaire G. Breathing disorders in Rett syndrome: progressive neurochemical dysfunction in the respiratory network after birth. *Respir Physiol Neurobiol*. 2009; 168(1–2):101–108. [PubMed: 19394452]
- Krakora D, Macrander C, Suzuki M. Neuromuscular junction protection for the potential treatment of amyotrophic lateral sclerosis. *Neurol Res Int*. 2012; 2012:Article 379657.
- Kumar P, Prabhakar N. Sensing hypoxia: carotid body mechanisms and reflexes in health and disease. *Respir Physiol Neurobiol*. 2007; 157(1):1–3. [PubMed: 17368118]
- Kuwahira I, Kondo T, Ohta Y, Yamabayashi H. Acute respiratory failure in multiple sclerosis. *Chest*. 1990; 97:246–248. [PubMed: 2295251]
- Kwiecien JM, O'Connor LT, Goetz BD, Delaney KH, Fletch AL, Duncan ID. Morphological and morphometric studies of the dysmyelinating mutant, the Long Evans shaker rat. *J Neurocytol*. 1998; 27(8):581–591. [PubMed: 10405025]
- Lane MA, Lee KZ, Salazar K, O'Steen BE, Bloom DC. Respiratory function following bilateral mid-cervical contusion injury in the adult rat. *Exp Neurol*. 2012; 235:197–210. [PubMed: 21963673]
- Lansing RW, Gracely RH, Banzett RB. The multiple dimensions of dyspnea: review and hypotheses. *Respir Physiol Neurobiol*. 2009; 167(1):53–60. [PubMed: 18706531]
- Lee KH, Yoon DH, Chung M-A, Sohn J-H, Lee H-J, Lee BH. Neuroprotective effects of mexiletine on motor evoked potentials in demyelinated rat spinal cords. *Neurosci Res*. 2010; 67:59–64. [PubMed: 20096736]
- Liu R, Narla RK, Kurinov I, Li B, Uckun FM. Increased hydroxyl radical production and apoptosis in PC12 neuron cells expressing the gain-of-function mutant G93A SOD1 gene. *Radiat Res*. 1999; 151(2):133–141. [PubMed: 9952297]
- Lladó J, Haengeli C, Pardo A, Wong V, Benson L, Coccia C, Rothstein JD, Shefner JM, Maragakis NJ. Degeneration of respiratory motor neurons in the SOD1 G93A transgenic rat model of ALS. *Neurobiol Dis*. 2006; 21(1):110–118. [PubMed: 16084734]
- Llewellyn-Smith IJ, Marin CL, Arnolda LF, Minson JB. Retrogradely transported CTB-saporin kills sympathetic preganglionic neurons. *NeuroReport*. 1999; 10:307–312. [PubMed: 10203327]
- Llewellyn-Smith IJ, Martin CL, Arnolda LF, Minson JB. Tracer-toxins: cholera toxin B-saporin as a model. *J Neurosci Methods*. 2000; 103:83–90. [PubMed: 11074098]
- Lovering AT, Fraigne JJ, Dunin-Barkowski WL, Vidruk EH, Orem JM. Tonic and phasic drive to medullary respiratory neurons during periodic breathing. *Respir Physiol Neurobiol*. 2012; 181(3): 286–301. [PubMed: 22484379]
- Lovett-Barr MR, Satriotomo I, Muir GD, Wilkerson JE, Hoffman MS, Vinit S, Mitchell GS. Repetitive intermittent hypoxia induces respiratory and somatic motor recovery after chronic cervical spinal injury. *J Neurosci*. 2012; 32(11):3591–3600. [PubMed: 22423083]
- Lunn KF, Fanarraga ML, Duncan ID. Myelin mutants: new models and new observations. *Microsc Res Tech*. 1995; 32(3):183–203. [PubMed: 8527854]
- Lyall RA, Donaldson N, Polkey MI, Leigh PN, Moxham J. Respiratory muscle strength and ventilatory failure in amyotrophic lateral sclerosis. *Brain*. 2001; 124(Pt 10):2000–2013. [PubMed: 11571218]

- MacFarlane PM, Mitchell GS. Episodic spinal serotonin receptor activation elicits long-lasting phrenic motor facilitation by an NADPH oxidase-dependent mechanism. *J Physiol.* 2009; 587(Pt 22): 5469–5481. [PubMed: 19805745]
- MacFarlane PM, Vinit S, Mitchell GS. Serotonin 2A and 2B receptor-induced phrenic motor facilitation: differential requirement for spinal NADPH oxidase activity. *Neuroscience.* 2011; 178:45–55. [PubMed: 21223996]
- Mansel JK, Normal JR. Respiratory complications and management of spinal cord injuries. *Chest.* 1990; 97(6):1446–1452. [PubMed: 2189697]
- Mantilla CB, Rowley KL, Fahim MA, Sieck GC. Synaptic vesicle cycling at type-identified diaphragm neuromuscular junctions. *Muscle Nerve.* 2004; 30:774–783. [PubMed: 15478121]
- Mantilla CB, Sieck GC. Neuromuscular adaptations to respiratory muscle inactivity. *Respir Physiol Neurobiol.* 2009; 169(2):133–140. [PubMed: 19744580]
- Mantilla CB, Sieck GC. Phrenic motor unit recruitment during ventilatory and non-ventilatory behaviors. *Respir Physiol Neurobiol.* 2011; 179:57–63. [PubMed: 21763470]
- Mantilla CB, Sieck GC. Neuromotor control in chronic obstructive pulmonary disease. *J Appl Physiol.* 2013 Epub ahead of print.
- Maskrey M, Evans SE, Masch U, Andersen NA, Sherrey JH. Phrenicotomy in the rat: acute changes in blood gases, pH and body temperature. *Respir Physiol.* 1992; 90(1):47–54. [PubMed: 1455098]
- Mayeux V, Corcia P, Besson G, Jafari-Schluep HF, Briolotti V, Camu W. N19S, a new SOD1 mutation in sporadic amyotrophic lateral sclerosis: no evidence for disease causation. *Ann Neurol.* 2003; 53(6):815–818. [PubMed: 12783432]
- McKay LC, Janczewski WA, Feldman JL. Sleep-disordered breathing after targeted ablation of preBötzing complex neurons. *Nat Neurosci.* 2005; 8(9):1142–1144. [PubMed: 16116455]
- McTigue DM, Horner PJ, Stokes BT, Gage FH. Neurotrophin-3 and brain-derived neurotrophic factor induce oligodendrocyte proliferation and myelination of regenerating axons in the contused adult rat spinal cord. *J Neurosci.* 1998; 18:5354–5365. [PubMed: 9651218]
- Mellies U, Lofaso F. Pompe disease: a neuromuscular disease with respiratory muscle involvement. *Respir Med.* 2009; 103(4):477–484. [PubMed: 19131232]
- Miller MJ, Haxhiu MA, Georgiadis P, Gudz TI, Kangas CD, Macklin WB. Proteolipid protein gene mutation induces altered ventilatory response to hypoxia in the myelin-deficient rat. *J Neurosci.* 2003; 23(6):2265–2273. [PubMed: 12657685]
- Mitchell, GS. Respiratory plasticity following intermittent hypoxia: a guide for novel therapeutic approaches to ventilatory control disorders. In: Gaultier, C., editor. *Genetic Basis for Respiratory Control Disorders.* New York: Springer Publishing Company; 2007. p. 291–311.
- Mitchell GS, Johnson SM. Neuroplasticity in respiratory motor control. *J Appl Physiol.* 2003; 94(1): 358–374. [PubMed: 12486024]
- Mochizuki A, Yamanouchi H, Murata M, Nagura H, Kuzuhara S, Toyokura Y. Medullary lesion revealed by MRI in a case of MS with respiratory arrest. *Neuroradiology.* 1988; 30:574–576. [PubMed: 3226547]
- Mothe AJ, Tator CH. Transplanted neural stem/progenitor cells generate myelinating oligodendrocytes and Schwann cells in spinal cord demyelination and dysmyelination. *Exp Neurol.* 2008; 213:176–190. [PubMed: 18586031]
- Mutulay FK, Gürses HN, Saip S. Effects of multiple sclerosis on respiratory functions. *Clin Rehabil.* 2005; 19(4):426–432. [PubMed: 15929512]
- Nagai M, Aoki M, Miyoshi I, Kato M, Pasinelli P, Kasai N, Brown RH Jr, Itoyama Y. Rats expressing human cytosolic copper-zinc superoxide dismutase transgenes with amyotrophic lateral sclerosis: associated mutations develop motor neuron disease. *J Neurosci.* 2001; 21(23):9246–9254. [PubMed: 11717358]
- Newsom-Davis J. Autonomous breathing: report of a case. *Arch Neurol.* 1974; 30:480. [PubMed: 4363791]
- Nicaise C, Hala TJ, Frank DM, Parker JL, Authalet M, Leroy K, Brion J-P, Wright MC, Lepore AC. Phrenic motor neuron degeneration compromises phrenic axonal circuitry and diaphragm activity in a unilateral cervical contusion model of spinal cord injury. *Exp Neurol.* 2012a; 235:539–552. [PubMed: 22465264]

- Nicaise C, Putatunda R, Hala TJ, Regan KA, Frank DM, Brion JP, Leroy K, Pochet R, Wright MC, Lepore AC. Degeneration of phrenic motor neurons induces long-term diaphragm deficits following mid-cervical spinal contusion in mice. *J Neurotrauma*. 2012b; 29(18):2748–2760. [PubMed: 23176637]
- Nichols NL, Gowing G, Satriotomo I, Nashold LJ, Dale EA, Suzuki M, Avalos P, Mulcrone PL, McHugh J, Svendsen CN, Mitchell GS. Intermittent hypoxia and stem cell implants preserve breathing capacity in a rodent model of ALS. *Am J Respir Crit Care Med*. 2013a; 187(5):535–542. [PubMed: 23220913]
- Nichols NL, Punzo AM, Duncan ID, Mitchell GS, Johnson RA. Cervical spinal demyelination with ethidium bromide impairs respiratory (phrenic) activity and forelimb motor behavior in rats. *Neuroscience*. 2012; 229:77–87. [PubMed: 23159317]
- Nichols NL, Vinit S, Mitchell GS. Intraleural CTB-saporin selectively kills phrenic motor neurons: a motor neuron disease model (abstract). *FASEB J*. 2013b
- Norenberg MD, Smith J, Marcilla A. The pathology of human spinal cord injury: defining the problems. *J Neurotrauma*. 2004; 21:429–440. [PubMed: 15115592]
- Ogier M, Katz DM. Breathing dysfunction in Rett syndrome: understanding epigenetic regulation of the respiratory network. *Respir Physiol Neurobiol*. 2008; 164(1–2):55–63. [PubMed: 18534925]
- Pal PK, Sathyaprabha TN, Tuhina P, Thennarasu K. Pattern of subclinical pulmonary dysfunctions in Parkinson's disease and the effect of levodopa. *Mov Disord*. 2007; 22(3):420–424. [PubMed: 17230476]
- Pandit C, Fitzgerald DA. Respiratory problems in children with Down syndrome. *J Paediatr Child Health*. 2012; 48(3):E147–152. [PubMed: 21535288]
- Pinto S, Gerales R, Vaz N, Pinto A, de Carvalho M. Changes of the phrenic nerve motor response in amyotrophic lateral sclerosis: longitudinal study. *Clin Neurophysiol*. 2009; 120(12):2082–2085. [PubMed: 19833553]
- Prabhakar NR. Sensory plasticity of the carotid body: role of the reactive oxygen species and physiological significance. *Respir Physiol Neurobiol*. 2011; 178(3):375–380. [PubMed: 21621009]
- Radtke C, Spies M, Sasaki M, Vogt PM, Kocsis JD. Demyelinating diseases and potential repair strategies. *Int J Dev Neurosci*. 2007; 25(3):149–152. [PubMed: 17408905]
- Redelings MD, McCoy L, Sorvillo F. Multiple sclerosis mortality and patterns of comorbidity in the United States from 1990 to 2001. *Neuroepidemiology*. 2006; 26:102–107. [PubMed: 16374035]
- Rice A, Fuglevand AJ, Laine CM, Fregosi RF. Synchronization of presynaptic input to motor units of tongue, inspiratory intercostal, and diaphragm muscles. *J Neurophysiol*. 2011; 105(5):2330–2336. [PubMed: 21307319]
- Richerson GB, Wang W, Hodges MR, Dohle CI, Diez-Sampedro A. Honing in on the specific phenotype(s) of central respiratory chemoreceptors. *Exp Physiol*. 2005; 90(3):259–266. [PubMed: 15728134]
- Rizvi SS, Ishikawa S, Faling LJ, Schlessinger L, Satia J, Seckel B. Defect in automatic respiration in a case of multiple sclerosis. *Am J Med*. 1974; 56:433–436. [PubMed: 4818409]
- Sallis ES, Mazzanti CM, Mazzanti A, Periera LA, Arroteia KF, Fustigatto R, Pelizzari C, Rodrigues A, Graça DL. OSP-Immunofluorescent remyelinating oligodendrocytes in the brainstem of toxically-demyelinated Wistar rats. *Arg Neuropsiquiatr*. 2006; 64(2A):240–244.
- Saywell SA, Ford TW, Meehan CF, Todd AJ, Kirkwood PA. Electrophysiological and morphological characterization of propriospinal interneurons in the thoracic spinal cord. *J Neurophysiol*. 2011; 105:806–826. [PubMed: 21106900]
- Schmid DA, Yang T, Ogier M, Adams I, Mirakhur Y, Wang Q, Massa SM, Longo FM, Katz DM. A TrkB small molecule partial agonist rescues TrkB phosphorylation deficits and improves respiratory function in a mouse model of Rett syndrome. *J Neurosci*. 2012; 32(5):1803–1810. [PubMed: 22302819]
- Schroth MK. Special considerations in the respiratory management of spinal muscular atrophy. *Pediatrics*. 2009; 123 (Suppl 4):S245–249. [PubMed: 19420154]

- Sendtner M, Holtmann B, Kolbeck R, Thoenen H, Barde YA. Brain-derived neurotrophic factor prevents the death of motoneurons in newborn rats after nerve section. *Nature*. 1992; 360:757–759. [PubMed: 1465147]
- Sherrey JH, Megirian D. After phrenicotomy the rat alters the output of the remaining respiratory muscles without changing its sleep-waking pattern. *Respir Physiol*. 1990; 81(2):213–225. [PubMed: 2148218]
- Sieck DC, Zhan WZ, Fang YH, Ermilov LG, Sieck GC, Mantilla CB. Structure-activity relationships in rodent diaphragm muscle fibers vs. neuromuscular junctions. *Resp Physiol Neurobiol*. 2012; 180:88–96.
- Sieck GC, Mantilla CB. Novel method for physiological recruitment of diaphragm motor units after upper cervical spinal cord injury. *J Appl Physiol*. 2009; 107:641–642. [PubMed: 19628723]
- Siegenthaler MM, Tu MK, Keirstead HS. The extent of myelin pathology differs following contusion and transection spinal cord injury. *J Neurotrauma*. 2007; 24(10):1631–1646. [PubMed: 17970626]
- Sperti S, Montanaro L, Mattioli A, Stirpe F. Inhibition by ricin of protein synthesis in vitro: 60S ribosomal subunit as the target of the toxin. *Biochem J*. 1973; 136:813–815. [PubMed: 4360718]
- Stewart H, Eisen A, Road J, Mezei M, Weber M. Electromyography of respiratory muscles in amyotrophic lateral sclerosis. *J Neurol Sci*. 2001; 191(1–2):67–73. [PubMed: 11676994]
- Stockley RA. Progression of chronic obstructive pulmonary disease: impact of inflammation, comorbidities and therapeutic intervention. *Curr Med Res Opin*. 2009; 25(5):1235–1245. [PubMed: 19335322]
- Talakad NS, Pradhan C, Nalini A, Thennarasu K, Raju TR. Assessment of pulmonary function in amyotrophic lateral sclerosis. *Indian J Chest Dis Allied Sci*. 2009; 51(2):87–91. [PubMed: 19445444]
- Tankersley CG, Haenggeli C, Rothstein JD. Respiratory impairment in a mouse model of amyotrophic lateral sclerosis. *J Appl Physiol*. 2007; 102(3):926–932. [PubMed: 17110520]
- Teeling JL, Perry VH. Systemic infection and inflammation in acute CNS injury and chronic neurodegeneration: underlying mechanisms. *Neuroscience*. 2009; 158(3):1062–1073. [PubMed: 18706982]
- Varma AK, Das A, Wallace G, Barry J, Vertegel AA, Ray SK, Banik NL. Spinal cord injury: a review of current therapy, future treatments, and basic science frontiers. *Neurochem Res*. 38:895–905. [PubMed: 23462880]
- Vinit S, Lovett-Barr MR, Mitchell GS. Intermittent hypoxia induces functional recovery following cervical spinal injury. *Respir Physiol Neurobiol*. 2009; 169(2):210–217. [PubMed: 19651247]
- Vinit S, Windelborne JA, Mitchell GS. Lipopolysaccharide attenuates phrenic long-term facilitation following acute intermittent hypoxia. *Respir Physiol Neurobiol*. 2011; 176(3):130–135. [PubMed: 21334467]
- Wong PC, Pardo CA, Borchelt DR, Lee MK, Copeland NG, Jenkins NA, Sisodia SS, Cleveland DW, Price DL. An adverse property of a familial ALS-linked SOD1 mutation causes motor neuron disease characterized by vacuolar degeneration of mitochondria. *Neuron*. 1995; 14(6):1105–1116. [PubMed: 7605627]
- Yan Q, Elliott J, Snider WD. Brain-derived neurotrophic factor rescues motor neurons from axotomy-induced cell death. *Nature*. 1992; 360:753–755. [PubMed: 1281520]
- Ye H, Buttigieg J, Wan Y, Wang J, Figley S, Fehlings MG. Expression and functional role of BK channels in chronically injured spinal cord white matter. *Neurobiol Dis*. 2012; 47(2):225–236. [PubMed: 22534235]
- Zhan WZ, Mantilla CB, Sieck GC. Regulation of neuromuscular transmission by neurotrophins. *Sheng Li Xue Bao*. 2003; 55(6):617–624. [PubMed: 14695476]
- Zhou L, Shine HD. Neurotrophic factors expressed in both cortex and spinal cord induce axonal plasticity after spinal cord injury. *J Neurosci Res*. 2003; 74:221–226. [PubMed: 14515351]

- Many neurological disorders disrupt spinal function and compromise breathing.
- Patients often maintain ventilatory capacity well after the onset of disease.
- Patients ultimately reach a point where compensation is no longer possible.
- We propose that a suite of mechanisms underlie compensatory respiratory plasticity.
- We contrast three rodent unique models of inspiratory motor dysfunction.

Figure 1.

Neuropathology underlying distinct, yet related neurological disorders reducing phrenic motor output. In *myelin disorders* (e.g. MS, upper panel), synaptic transmission to respiratory motor neurons is abnormal in demyelinated pathways (faded input to motor neurons). Asynchronous (or even reduced) synaptic activation of phrenic motor neurons subsequently impairs phrenic nerve activity (Johnson et al., 2010; Nichols et al., 2012). With *motor neuron disease* (e.g. ALS, middle panel), functional motor units are lost (faded motor neuron on right). Although spared motor units are capable of induced plasticity, the capacity to increase phrenic nerve activity remains decreased from normal (Nichols et al., 2013a). *During spinal cord injury*, there is traumatic disruption and/or degeneration of spinal neural pathways to respiratory motor neurons (faded synapse on left), accompanied by varied degrees of respiratory motor neuron death (faded neuron on right). Phrenic nerve output ipsilateral to the injury remains impaired after mid-cervical contusion injuries (Golder et al., 2011). In each of these cases, ventilatory capacity is completely preserved despite significant impairment in phrenic motor output (see Figure 2). At some point, the injury and/or disease progression can reach a level where such effective compensation is no longer possible, at which time patients may seem to just “fall off a cliff” into ventilatory failure.

Figure 2.

Tidal volume and integrated phrenic nerve amplitude (mean±SEM) in three models of neurological disease: 1) demyelination of spinal segment C₂ with unilateral intraspinal ethidium bromide injections (EB), 2) motor neuron disease in the SOD1^{G93A} mutant rat, a model that mimics the pathophysiology and clinical signs of humans with familial ALS (SOD1), and 3) unilateral spinal cord contusion injury at spinal segment C₄ (SCI). Although the ability to generate adequate tidal volume (V_T) in response to chemosensory activation (hypercapnia) is maintained in each simulated disorder, integrated phrenic nerve amplitude is significantly decreased (*p<0.05). Thus, an impressive degree of compensatory plasticity must be present for rats to generate normal inspiratory volumes. With significant neuromotor deficits in phrenic output, compensation must occur “downstream”, either at the site of neuromuscular transmission or at the muscle itself, or in “parallel” by greater utilization of alternate respiratory muscles. Note that the EB V_T data are normalized to body mass, making the overall values appear lower than V_T from SOD1 and SCI studies. Data adapted from Golder et al., 2011 and Nichols et al., 2012, 2013a. Integrated phrenic amplitude is expressed in voltage, similar to previously published data (Nichols et al., 2013a, supplemental material).

Figure 3.

Hypothesis of multilayered mechanisms giving rise to compensatory respiratory plasticity associated with diverse pathologies (demyelination, motor neuron death, and contusion). Rats preserve ventilatory capacity despite severe injury (*e.g.* contusion or demyelination) or until late in disease progression (ALS; Figure 2). We suggest that human patients use a similarly comprehensive, multilayered strategy to compensate for severe CNS pathology, thereby preserving breathing capacity; failure to compensate for neurological disorders would lead to rapid death. Potential mechanisms include: (1) increased central respiratory drive to motor neurons (green), (2) strengthened neural (synaptic) inputs to phrenic motor neurons (purple), (3) plasticity within respiratory muscles or neuromuscular junctions (red), and (4) shifts in the balance of respiratory muscles contributing to breathing from more severely compromised to less compromised respiratory motor neuron pools (blue arrow). The fourth mechanism represents an emergent property (*i.e.* collective response) from the first three “layers” of respiratory compensation.